

REMARKS

The Official Action dated June 22, 2010 has been carefully considered. Accordingly, the present Amendment is believed sufficient to place the present application in condition for allowance. Reconsideration is respectfully requested.

By the present Amendment, claim 21 is amended to more clearly recite a method for percutaneously transferring a remedy for ophthalmic disease to an external ophthalmic tissue comprising at least one of conjunctiva, lacrimal tissue and cornea and having a disease condition selected from the group consisting of ocular infection of conjunctiva, lacrimal tissue and cornea, allergic conjunctivitis, pollinosis, vernal conjunctivitis, conjunctivitis, blepharitis, keratitis, corneal tumor, dacryocystitis, superficial keratitis, marginal blepharitis, scleritis, holdeolum, tarsadenitis, and trachoma, and that the remedy is for treatment of the disease, as set forth throughout the specification. It is believed that these changes do not involve any introduction of new matter, whereby entry is believed to be in order and is respectfully requested.

In the Official Action, claims 2-5, 8-15, and 21-23 were rejected under 35 U.S.C. §102(b) as being anticipated by the Tojo et al PCT Publication WO 01/26648 and its corresponding U.S. Patent No. 7,052,714. In response to Applicants' previous arguments, the Examiner asserted that the previous arguments are directed to methods of treatment and targeted treatment and are not commensurate in scope with the claims directed to a method of transferring a drug from the patch to the skin and tissue. The Examiner further asserted that the application of the transdermal device of Tojo et al inherently results in the claimed method and transfers the drugs through the skin and tissue with the claimed permeation recitations.

However, Applicants submit that the method of claim 21, and the methods of claims 2-5, 8-15, 22 and 23 dependent thereon, are not anticipated by and are patentably distinguishable

from Tojo et al. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

More particularly, as defined by claim 21, the present invention is directed to a method for percutaneously transferring a remedy for ophthalmic disease to an external ophthalmic tissue comprising at least one of conjunctiva, lacrimal tissue and cornea and having a disease condition selected from the group consisting of ocular infection of conjunctiva, lacrimal tissue and cornea, allergic conjunctivitis, pollinosis, vernal conjunctivitis, conjunctivitis, blepharitis, keratitis, corneal tumor, dacryocystitis, superficial keratitis, marginal blepharitis, scleritis, holdeolum, tarsadenitis, and trachoma. Thus, the transfer is to an external ophthalmic tissue (1) comprising at least one of conjunctiva, lacrimal tissue and cornea, and (2) having a disease condition selected from the recited group, and the remedy is for treatment of the disease. The method comprises applying a pressure-sensitive adhesive tape preparation comprising a plaster layer provided on a support, to a front skin surface of an upper eyelid and/or a lower eyelid to transfer the remedy for ophthalmic disease in the plaster layer to the external ophthalmic tissue by percutaneous permeation in such a manner that the remedy for ophthalmic disease is transferred by percutaneous permeation to the external ophthalmic tissue from the skin surface. The plaster layer contains the remedy for ophthalmic disease and a pressure-sensitive adhesive. The amount, in units of $\mu\text{g/g-tissue}$, of the remedy transferred by percutaneous permeation to the external ophthalmic tissue by the application within 8 hours after the application amounts to at least twice as much as the amount of the remedy transferred to the external ophthalmic tissue through a systemic blood flow.

The method of claim 21 differs from that of Tojo et al in at several important respects, including the target site to which the remedy is transferred, the remedy for ophthalmic disease

which is transferred, the method by which the remedy is predominantly transferred, and the unintended transfer to the non-targeted site. More specifically, Tojo et al is directed to an ophthalmic transdermal patch for treating diseases of the posterior segment of the eye, i.e., the lens, the vitreous body, the choroids and the retina (see, for example, column 1, lines 6-9). Tojo et al teach that their patch delivers drug to blood plasma which in turn delivers the drug to the posterior segment of the eye (see the in vivo test results at columns 12-13).

Thus, while Tojo et al teach transfer of a remedy for a disease of the posterior segment of the eye, the method of claim 21 is directed to a method for the transfer of a remedy for an ophthalmic disease to an external ophthalmic tissue, i.e., to an external ophthalmic tissue (1) comprising at least one of conjunctiva, lacrimal tissue and cornea, and (2) having a disease condition selected from the recited group. Applicants find no teaching by Tojo et al of the percutaneous transfer of a remedy for an ophthalmic disease to an external ophthalmic tissue comprising at least one of conjunctiva, lacrimal tissue and cornea having a disease condition selected from the recited group. In fact, Tojo et al is not concerned with transfer of a remedy to external ophthalmic tissue having a disease condition selected from the group recited in claim 21, and Tojo et al, to the contrary, mention use of eye drops in the Background portion of the application as sufficient for providing therapeutically effective drug levels in the anterior segment of the eye (see column 1, lines 16-20). Tojo et al's device is for transfer to the posterior segment of the eye, i.e., the lens, the vitreous body, the choroids and the retina, having diseases other than those recited in claim 21, as set forth at column 7, lines 4-24 of Tojo et al.

The Examiner has previously asserted that the claimed method is inherent in the teachings of Tojo et al. However, none of the methods disclosed by Tojo et al transfer a remedy to a external ophthalmic tissue comprising at least one of conjunctiva, lacrimal tissue and cornea

having a disease condition selected from ocular infection of conjunctiva, lacrimal tissue and cornea, allergic conjunctivitis, pollinosis, vernal conjunctivitis, conjunctivitis, blepharitis, keratitis, corneal tumor, dacryocystitis, superficial keratitis, marginal blepharitis, scleritis, holdeolum, tarsadenitis, and trachoma. Thus, the method of claim 21 is not inherent in any of the teachings of Tojo et al.

Additionally, according to Tojo et al, the remedy is transferred to the application site by percutaneous absorption, after which the drug is transferred into the blood to administer the drug to the posterior segment of the eye from the plasma in the blood through the systemic blood flow. For example, the Tojo et al test results examine both the plasma concentration and posterior eye concentration of active ingredient. Tojo et al indicate that the prednisolone amount was determined in the plasma and the eyeball of the rats to which were applied a 3% prednisolone-containing preparation, P5 and, as a result, 70 ng/g prednisolone was detected 6 hours after the application of the preparation, indicating that prednisolone was transferred to the interior of the eye at a concentration that was equivalent to 18% of the plasma concentration (Table 8, column 12, line 64-column 13, line 7). Additionally, Tojo et al disclose in Table 8 that 7.2 ng/g of SJA6017 was detected in the eyeball 12 hours after the application of the SJA6017-containing preparation, reaching about 16% of the plasma concentration of the drug, which is higher than the corresponding value (13%) detected after intravenous application. Tojo et al conclude that this method of administration of a drug by transdermal patches is a method available to continuously transfer a drug from the plasma into the eyeball (column 13, lines 39-48).

In contrast, according to the method of claim 21, the predominate transfer of remedy to the target site is through percutaneous permeation, i.e., the amount, in units of $\mu\text{g/g-tissue}$, of the

remedy transferred by percutaneous permeation to the external ophthalmic tissue by the application within 8 hours after the application amounts to at least twice as much as the amount of the remedy transferred to the external ophthalmic tissue through a systemic blood flow. In fact, in specific embodiments of the present invention, little or no drug is transferred from plasma to the target site of the external ophthalmic tissue. For example, as set forth in the present specification:

"It is further apparent that the concentration of the drug in the conjunctivae of the other eye than the eye, to the eyelids of which the preparation has been applied is clearly lower than that in the eye patched, and that since the concentration of the drug in the plasma was lower than the detection limit value ($< 0.005 \mu\text{g/mL}$), the drug is percutaneously transferred to the conjunctivae from the eyelid parts, to which the preparation is applied, rather than the transfer to the conjunctivae through the systemic blood flow when the preparation is applied to the eyelid parts." (page 45, line 19-page 46, line 2).

"Even from the experimental results shown in Table 6, it is apparent that the transfer of the drug to the anterior ocular segment (conjunctiva, lacrimal tissue, etc.) from the transdermal drug delivery system for treatment of ophthalmic diseases according to the present invention is conducted by percutaneous transfer from the applied site rather than the transfer through the systemic blood flow." (page 48, lines 14-21).

Thus, the predominate mechanism of transfer as claimed is significantly distinguishable from that of Tojo et al.

Finally, because the predominate mechanism of transfer of the agent in the method according to claim 21 is, as claimed, by percutaneous permeation, rather than systemic transfer from plasma, it is apparent that administration of the agent to body sites other than the diseased site are minimal according to the present methods. In contrast, in the method of Tojo et al, the systemic distribution of the agent to the target site of the posterior segment of the eye also undesirably results in systemic distribution of the agent throughout the body. As it is an object of Tojo et al to increase drug concentration in the plasma and, as a result, systemic administration of the drug, such systemic administration which will occur in not only the desired

target site of the posterior segment of the eye, but also other body areas, potentially causing unwanted side effects. This disadvantage is avoided by the present methods.

As shown in Table 1 in the present specification, the transdermal drug delivery method for treatment of ophthalmic diseases according to the present invention (Example 1) was recognized to have high transferability of ketotifen fumarate to the conjunctiva over a long period of time while, in contrast, it was demonstrated that an eye drop ophthalmic solution (Comparative Example 1) is rapidly washed out by tears, and only a small amount of the drug remains 1 hour after administration, and whereby potency over a long period of time cannot be expected (page 38, lines 9-18). The present methods therefore have a significant advantage over the use of eye drops, the method taught by Tojo et al as adequate for administering a remedy to an external ophthalmic tissue.

Additionally, while Tojo et al disclose that their preparations may be used to deliver drugs to the eye through the skin and other parts of the body and that the ophthalmic transdermal patches may be applied at any location of the body surface as desired, on a site relatively close to the eye, e.g., on the temple or around the eye, in particular on the skin of the eyelids or next to the lateral angle of the eye, the in-vivo examples of Tojo et al employ the patches on the abdominal skin (column 9, lines 11 and 45) and on “the skin of the animals” (column 12, lines 35-39). Moreover, since Tojo et al are concerned with systemic drug delivery, one of ordinary skill in the art would not expect the location of the Tojo et al patch to significantly effect the systemic drug delivery.

Further, while Tojo et al broadly refer to application to the eyelids, an example thereof is not provided and there is no recognition that application to an eyelid transfers a drug to external ophthalmic tissue having a disease as claimed in an amount of at least twice as much as is

delivered systemically over an eight-hour period as recited in claim 21. In view of the failure of Tojo et al to exemplify application of a transdermal patch to an eyelid having a disease as claimed, particularly to transfer a remedy for treatment of the disease, and in view of the unexpected and unpredictable increased drug transfer by percutaneous permeation as compared with systemic administration in the present method, the advantages of the method of claim 21 are unpredictable in the teachings of Tojo et al.

Moreover, a comparison test between a method according to the present invention wherein a preparation as claimed is applied to upper and lower eyelid parts and a method as exemplified in Tojo et al wherein a preparation is applied to the back is also described in the present specification:

“As apparent from the results shown in Table 4, it is understood that when the transdermal drug delivery system for treatment of ophthalmic diseases according to the present invention is applied to the skin of the back of the subject animal, the amount of the drug (ketotifen fumarate) penetrated into the skin surface under the application, absorbed in an intraepithelial blood capillary and reached the conjunctivae of both eyes through the systemic blood flow from the blood capillary is at the level of about 0.01 to 0.02 $\mu\text{g/g}$ even when 4 hours, 8 hours and 24 hours have elapsed from the application, namely, the amount of the drug transferred to the ophthalmic topical tissues (conjunctivae of the external ophthalmic tissues) through the systemic blood flow is extremely little.

On the contrary, it is understood that when the transdermal drug delivery system for treatment of ophthalmic diseases according to the present invention is applied to the skin surfaces of the upper and lower eyelids, the drug is transferred to the conjunctivae under the application at a concentration as high as 4.44 $\mu\text{g/g}$ after 4 hours from the application, and the amount transferred retain high levels of 2.95 $\mu\text{g/g}$ after 8 hours and 0.13 $\mu\text{g/g}$ after 24 hours.” (from page 43, line 17 to page 44, line 7).

Thus, the present methods of transferring a remedy to the external ophthalmic tissue including the conjunctiva, lacrimal tissue and cornea by percutaneous permeation have a surprising and significant advantage over the method exemplified by Tojo et al, and this advantage is neither recognized nor suggested by Tojo et al. The present methods have additional advantages as well. Efficacy of the remedy for ophthalmic disease is achieved faster as the

percutaneous permeation delivers the remedy to the external ophthalmic tissue of the eye faster than it would be delivered through systemic blood flow. As a higher amount of the applied drug is delivered to the external ophthalmic tissue by percutaneous permeation as compared with delivery through systemic blood flow, even a drug low in percutaneous permeability can be administered in an amount sufficient to provide efficacy. Further, even when the remedy is a drug having skin irritability, efficacy and a reduction of skin irritability can be reconciled by controlling percutaneous absorbability and the amount permeating the skin. Finally, as noted above, problems with systemic drug delivery, including undesirable side effects, can be reduced or eliminated, and the efficacy of the remedy can be sustained over a long period of time. These advantages are demonstrated in the Examples in the present specification.

While the Examiner asserted in the Official Action that Applicants' previous arguments regarding treatment were not commensurate with the scope of the claims reciting transfer of remedy, Applicants submit that the present arguments are specific to transfer of a remedy as claimed. Important features of the claimed transfer method include, *inter alia*, the target site, i.e., external ophthalmic tissue having a recited disease, and the amount of remedy which is transferred, i.e., the amount, in units of $\mu\text{g/g}\cdot\text{tissue}$, of the remedy transferred by percutaneous permeation to the external ophthalmic tissue by the application within 8 hours after the application amounts to at least twice as much as the amount of the remedy transferred to the external ophthalmic tissue through a systemic blood flow. While anticipation under 35 U.S.C. §102 requires that each and every element as set forth in the claims is found, either expressly or inherently described, in a single prior art reference, *In re Robertson*, 169 F.3d 743 (Fed. Cir. 1999), Tojo et al do not disclose, expressly or inherently, a remedy transfer method to a target site as claimed or the amount of remedy transferred by percutaneous permeation to the external

ophthalmic tissue as claimed. Thus, Tojo et al do not describe each and every element of the present claim 21 transfer method and therefore do not anticipate claim 21. The rejection under 35 U.S.C. §102(b) is therefore overcome. Reconsideration is respectfully requested.

Claims 2-6, 8-15 and 21-23 were rejected under 35 U.S.C. §103(a) as being unpatentable over the Higo et al U.S. Patent No. 5,866,157 in view of the Trimming et al U.S. Patent Publication No. 2001/0006968, Tojo et al, and the Lerner et al PCT Publication WO 97/18855. The Examiner again asserted that the arguments in Applicants' previous response were directed to methods of treatment and targeted treatment and are not commensurate in scope with the claims directed to a method of transferring a drug from the patch to the skin and tissue and that such a method of transfer is intrinsic to the application of transdermal devices. The Examiner further asserted that the secondary references are properly relied on for the respective teachings the Examiner has indicated.

However, Applicants submit that claims 2-6, 8-15 and 21-23 are not rendered obvious over, and are patentably distinguishable from, the combination of Higo et al, Trimming et al, Tojo et al and Lerner et al. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

More particularly, as discussed in detail above, the present invention is directed to a method for percutaneously transferring a remedy for ophthalmic disease to an external ophthalmic tissue comprising at least one of conjunctiva, lacrimal tissue and cornea and having a disease condition selected from the group consisting of ocular infection of conjunctiva, lacrimal tissue and cornea, allergic conjunctivitis, pollinosis, vernal conjunctivitis, conjunctivitis, blepharitis, keratitis, corneal tumor, dacryocystitis, superficial keratitis, marginal blepharitis, scleritis, holdeolum, tarsadenitis, and trachoma. Thus, the transfer is to an external ophthalmic

tissue (1) comprising at least one of conjunctiva, lacrimal tissue and cornea, and (2) having a disease condition selected from the recited group. The method comprises applying a pressure-sensitive adhesive tape preparation comprising a plaster layer provided on a support, to a front skin surface of an upper eyelid and/or a lower eyelid to transfer the remedy for ophthalmic disease in the plaster layer to the external ophthalmic tissue by percutaneous permeation in such a manner that the remedy for ophthalmic disease is transferred by percutaneous permeation to the external ophthalmic tissue from the skin surface. The plaster layer contains the remedy for ophthalmic disease and a pressure-sensitive adhesive. The amount, in units of $\mu\text{g/g}\cdot\text{tissue}$, of the remedy transferred by percutaneous permeation to the external ophthalmic tissue by the application within 8 hours after the application amounts to at least twice as much as the amount of the remedy transferred to the external ophthalmic tissue through a systemic blood flow.

Higo et al disclose matrix type patch formulations which allow the physiological active substance to be absorbed via skin continuously into the circulating blood (column 6, lines 29-31). Test example 1 at column 16 applies patches to thawed human abdominal skin while Test example 2 at column 17 applies patches to normal human skin in the back region. Applicants find no teaching by Higo et al relating to transferring a remedy to an external ophthalmic tissue (1) comprising at least one of conjunctiva, lacrimal tissue and cornea, and (2) having a disease condition selected from the recited group, particularly for percutaneous transfer. Similarly, Applicants find no teaching or suggestion by Higo et al to apply a patch to a front skin surface of an upper eyelid and/or lower eyelid as presently claimed. Moreover, as Higo et al is concerned with delivering an active to blood for different diseases than recited in claim 21, the improvements of the present invention in delivering the remedy to the external ophthalmic tissue having a disease from the group defined in claim 21 in a greater amount than through systemic

blood flow delivery according to the present invention is neither recognized nor predictable in view of Higo et al. Specifically, Higo et al provide no teaching, suggestion or recognition that the amount, in units of $\mu\text{g/g}$ tissue, of the remedy transferred by percutaneous permeation to the external ophthalmic tissue by the application within 8 hours after the application according to the present method amounts to at least twice as much as the amount of the remedy transferred to the external ophthalmic tissue through a systemic blood flow.

The Examiner asserted that the claimed method of transfer is intrinsic to the application of transdermal devices. However, as Higo et al do not disclose application of a patch to a front skin surface of an upper eyelid and/or lower eyelid as presently claimed, the presently claimed methods are not inherent in the teachings of Higo et al. Moreover, as neither Higo et al nor the secondary references teach that the remedy transferred by percutaneous permeation to the external ophthalmic tissue by the application as claimed within 8 hours after the application amounts to at least twice as much as the amount of the remedy transferred to the external ophthalmic tissue through a systemic blood flow, the advantages of the present transfer methods are surprising and unpredictable over the cited combination of references.

In this regard, the Examiner's attention is again directed to the results of Example 3 in the present specification as follows:

“As apparent from the results shown in Table 4, it is understood that when the transdermal drug delivery system for treatment of ophthalmic diseases according to the present invention is applied to the skin of the back of the subject animal, the amount of the drug (ketotifen fumarate) penetrated into the skin surface under the application, absorbed in an intraepithelial blood capillary and reached the conjunctivae of both eyes through the systemic blood flow from the blood capillary is at the level of about 0.01 to 0.02 $\mu\text{g/g}$ even when 4 hours, 8 hours and 24 hours have elapsed from the application, namely, the amount of the drug transferred to the ophthalmic topical tissues (conjunctivae of the external ophthalmic tissues) through the systemic blood flow is extremely little.

On the contrary, it is understood that when the transdermal drug delivery system for treatment of ophthalmic diseases according to the present invention is applied to the skin surfaces of the upper and lower eyelids, the drug is transferred to the conjunctivae under the application at a concentration as high as 4.44 $\mu\text{g/g}$ after 4 hours from the application, and the amount transferred retain high levels of 2.95 $\mu\text{g/g}$ after 8 hours and 0.13 $\mu\text{g/g}$ after 24 hours." (page 43, line 17 to page 44, line 16).

This Example therefore demonstrates the important advantages of the present transfer method over the exemplary teachings of Higo et al and particularly that the remedy can be transferred to the target site at a higher concentration over a long period of time.

Trimming et al teach an ophthalmic composition, for example, eye drops, comprising ketotifen for treatment of allergic conjunctivitis is compatible with soft contact lens (paragraph [0003]). Thus, while Higo et al are directed to systemic administration compositions, Trimming et al are directed to eye drops. One of ordinary skill in the art would have had no reason to combine any of the systemic administration composition teachings of Higo et al with the eye drops of Trimming et al as these two references relate to different administration routes and mechanisms and neither reference teaches, suggests or recognizes that application of a pressure-sensitive adhesive tape preparation to a front skin surface of an upper eyelid and/or a lower eyelid as presently claimed transfers a remedy for ophthalmic disease to an external ophthalmic tissue by percutaneous permeation.

Tojo et al, as discussed above, discloses devices for transferring a remedy to plasma for systemic delivery to the posterior segment of the eye. While Tojo et al disclose that their preparations may be used to deliver drugs to the eye through the skin and other parts of the body and that the ophthalmic transdermal patches may be applied at any location of the body surface as desired, on a site relatively close to the eye, e.g., on the temple or around the eye, in particular on the skin of the eyelids or next to the lateral angle of the eye, Tojo et al fail to disclose

application to an external ophthalmic tissue (1) comprising at least one of conjunctiva, lacrimal tissue and cornea, and (2) having a disease condition selected from the recited group of claim 21. Additionally, the in-vivo examples of Tojo et al, like those of Higo et al, employ the patches on the abdominal skin (column 9, lines 11 and 45) and on “the skin of the animals” (column 12, lines 35-39).

Moreover, since Tojo et al are concerned with systemic drug delivery, one of ordinary skill in the art would not expect the location of the Tojo et al patch to significantly effect the systemic drug delivery. Thus, Tojo et al, like Higo et al, fail to recognize that application to an eyelid transfers a remedy to external ophthalmic tissue having a disease as recited in claim 21 in an amount of at least twice as much as is delivered systemically over an eight-hour period as recited in claim 21. To the contrary, Tojo et al indicate that eye drops are satisfactory for treating external ophthalmic conditions. In view of the failure of Tojo et al to exemplify application of a transdermal patch to an eyelid, particularly to transfer a remedy to an external ophthalmic tissue having a disease as recited in claim 21, and in view of the unexpected and unpredictable increased drug transfer by percutaneous permeation as compared with eye drops and systemic administration, the method of claim 21 is not suggested by the teachings of Tojo et al in combination with Higo et al.

Finally, Lerner et al disclose an iontophoresis device for enhancing the delivery of a drug into a selected organ or tissue, for example the brain, which device includes special electrodes connected with a selected energy source which maintains an energy field before and during the delivery of the drug. Beginning at page 37, line 34, Lerner et al disclose an embodiment for intracerebral transocularis wherein iontophoresis is conducted through the eyeballs. As noted by the Examiner, Lerner et al disclose that skin of the eyelid has a resistance lower than that on the

rest of the skin surface and a resistance of the cornea and of the sclera is negligible. It is apparent that Lerner et al are referring to resistance to the flow of current, as Lerner et al further indicate that in this method, a split active electrode must be placed over the eyes and is covered by cotton or other material wetted in the solution of the necessary active substance and touching the skin as the electrodes themselves must not touch the skin, another split electrode covered by cotton or other material and wetted in the water is fixed on the mastoid processors or on another place or a single passive electrode is fixed on the back of the head in the area of cervical vertebrae or on another place, and, depending on individual tolerance (pressure or some other unpleasant feelings), current intensity can increase up to 10 mA (page 38, lines 2-18).

Thus, Lerner et al are concerned with administration of a drug to the brain by bypassing the blood-brain barrier using iontophoresis. One of ordinary skill in the art would have had no apparent reason to combine any of the teachings of Lerner et al with either the systemic administration compositions of Higo et al or Tojo et al, or the eye drops of Trimming et al. Lerner et al's teaching of the resistance of the eyelids to the flow of current is simply irrelevant to the systemic administration of Higo et al and Tojo et al and to Trimming et al's eye drops.

In determining patentability under 35 U.S.C. §103, it is necessary to determine whether there was an apparent reason to combine the known elements of the prior art in the fashion of the claims at issue, *KSR International Co. v. Teleflex, Inc.*, 550 US 398, 418 (2007). Neither Higo et al nor Tojo et al teach a method for transferring a remedy for ophthalmic disease to an external ophthalmic tissue having a disease as recited in claim 21. Additionally, as Trimming et al and Lerner et al are directed to different and distinct modes of administration of actives, and none of these references provide any teaching of a method for percutaneously transferring a remedy to an external ophthalmic tissue having a disease selected from the group recited in claim 21, these

references cannot be properly combined to result in the method of claim 21. Accordingly, combination of these references does not provide any apparent reason to one of ordinary skill in the art to have combined their elements in a manner that renders the method of claim 21 obvious, and the rejection under 35 U.S.C. §103 is therefore overcome. Reconsideration is respectfully requested.

Finally, claims 2-5, 8-15 and 21-23 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 3-7, 11 and 48 of copending application Serial No. 10/569,772 in view of Tojo et al. This rejection is traversed and reconsideration is respectfully requested.

Claim 21 is directed to a method for percutaneously transferring a remedy for ophthalmic disease to an external ophthalmic tissue comprising at least one of conjunctiva, lacrimal tissue and cornea and having a disease condition selected from the group consisting of ocular infection of conjunctiva, lacrimal tissue and cornea, allergic conjunctivitis, pollinosis, vernal conjunctivitis, conjunctivitis, blepharitis, keratitis, corneal tumor, dacryocystitis, superficial keratitis, marginal blepharitis, scleritis, holdeolum, tarsadenitis, and trachoma. The claims of copending application Serial No. 10/569,772 are directed to methods of promoting lacrimal fluid secretion. Applicants submit that the copending application methods of promoting lacrimal fluid secretion are distinct and nonobvious over methods for percutaneously transferring a remedy for ophthalmic disease to an external ophthalmic tissue comprising at least one of conjunctiva, lacrimal tissue and cornea and having a disease condition selected from the group of claim 21. The respective claims are therefore directed to distinct therapies, whereby the rejection should be withdrawn. Reconsideration is respectfully requested. Moreover, in the event that the provisional double patenting rejection is the only rejection remaining in the present application,

the rejection should be withdrawn in the present application, thereby permitting the present application to issue as a patent, MPEP §804.

It is believed that the above represents a complete response to Official Action, and places the present application in condition for allowance. In the event there are any outstanding issues relating to this application, the Examiner is urged to telephone the undersigned to efficiently resolve the same. Reconsideration and an early allowance are requested.

Please charge any fees required in connection with the present communication, or credit any overpayment, to Deposit Account No. 503915.

Respectfully submitted,

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